REMARKS

Claims 1, 3-42, and 46-48 are pending in the instant application. Claim 14 has been cancelled to remove reference to subject matter previously removed from claim 1, from which claim 14 depends. Claims 15 and 16 have been amended. Accordingly, claims 1, 3-13, 15-42, and 46-48 will be pending in the application upon entry of the instant amendment. *No new matter has been added.*

Claims 15-16 were amended to adjust the dependency from cancelled claim 14 to dependency from claim 1 (from which claim 14 depended). Support for the amendment of the claims can be found throughout the specification and claims as originally filed. In particular, support for the amendment of claims 15 and 16 can be found in claims 15 and 16, respectively, as originally filed.

Amendment and/or cancellation of the claims at any time during the prosecution of this application are not to be construed as acquiescence to any of the objections/rejections set forth in the instant Office Action or any previous Office Action, and are done solely to expedite prosecution of the application. Applicants submit that claims were not added or amended during the prosecution of the instant application for reasons related to patentability. Applicants reserve the right to pursue the claims as originally filed, or similar claims, in this or one or more subsequent patent applications.

Duplicate Claims

Claims 20-34 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 1 and 19. While Applicants have previously stated that this issue will be addressed upon allowance of claims 1 and 19, Applicants respectfully traverse this objection as unfounded.

Applicants assert that the reasoning for this objection is at the heart of the misunderstanding the Examiner has regarding the difference between a compound and an autoinducer molecule. In this regard, Applicants respectfully point out that an autoinducer molecule of the invention is ***always*** a compound of formula (I), ***while the reverse is not true***, *i.e.*, all compounds of formula (I) are not autoinducer molecules. Moreover, as stated in Applicants' response of July 11, 2003, claims 1-19 are directed to compounds *per se* (*i.e.*, regardless of use)

while claims 20-34 are directed to the autoinducer molecules that fall within formula I of claim 1. As such, it cannot be stated that these claims are "duplicates" or that they "are so close in content that they cover the same thing." The claims clearly do not cover the same content.

Claim Rejections - 35 U.S.C. §112

Rejection of Claims under 35 U.S.C. §112, First Paragraph

The Office Action maintains that the specification is only enabling for making and using 2-heptyl-3-hydroxy-4-quinolone and rejects claims 1-42, and 46-48 under 35 U.S.C. §112, first paragraph. Applicants respectfully traverse the rejection and reiterate herein the arguments presented in Applicants' response of July 11, 2003.

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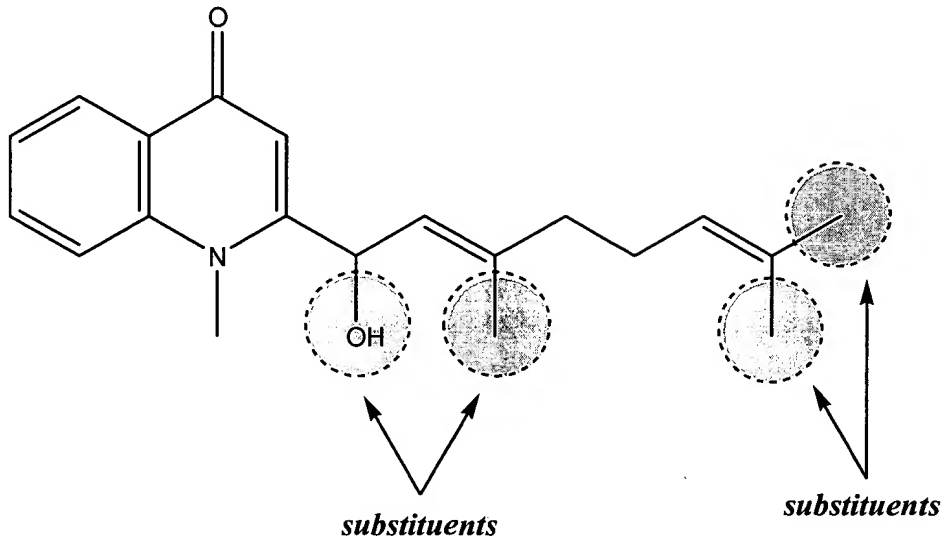
The Office Action asserts that a general procedure for making the compounds of the instant invention has not been provided and that starting materials for making the instant compound other than 2-heptyl-3-hydroxy-4-quinolone (especially those compounds wherein R_{10}-R_{24} are other than hydrogen and wherein R_2-R_4 are all halogen), "are not seen in the specification, but are required."

Applicants, again, respectfully refer the Examiner to the references cited in the Office Action of September 9, 2002, which, while they do not encompass the claims or the claimed compounds of the invention, ***are indicative of the vast body of knowledge that would have been available to the ordinarily skilled artisan at the time of filing of the present application for the preparation of related quinolone compounds.*** The Office Action, states on page 2 that "the substituents in the compound of Giulhon or Dekker are unsubstituted alkyl or alkenyl, whereas the instant heptyl may have up to 15 different substituents." Applicants respectfully disagree with this analysis

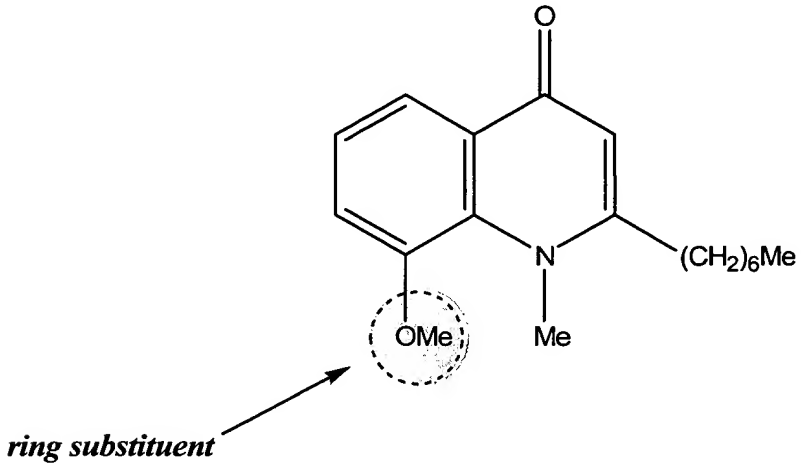
In this regard, the Examiner's attention is invited to Dekker et al, columns 8 and 9, wherein compounds CJ-13,136, CJ-13,217, CJ-13,536, CJ-13,564, CJ-13,565, CJ-13,566, CJ-13,567, and CJ-13,568 are depicted with substituents (such as epoxy, hydroxyl, alkyl, or derivatization with a double bond) from an octyl side chain, *i.e.*, a methyl derivatized heptyl. For

example, compound "CJ-13,567," of Dekker et al. is shown below with an indication of the substituents on the alkylene-substituted quinolones.



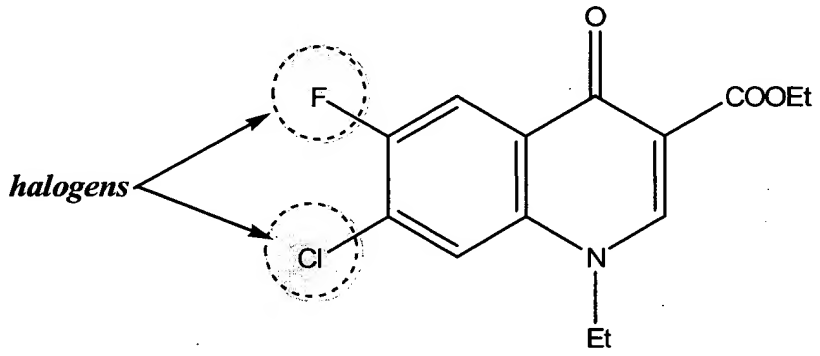
Dekker et al

The Examiner's attention is also respectfully directed to Guilhon et al., page 1193, compounds 3a-3c, where the quinolone compound is substituted on the ring with a methoxy, *i.e.*, R_4 of formula I of claim 1 of the instant invention. For example, compound 3c, on page 1193 is



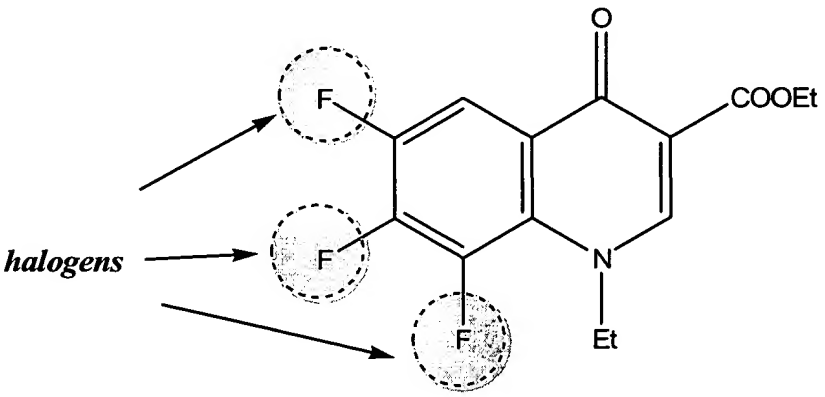
Guilhon et al.,

Furthermore, it was Applicants' contention that the references provided by the Office Action of September 9, 2002, were indicative of the body of art representative of the quinolone synthesis art, but by no means, the sole collection of art directed to the synthesis of quinolone compounds. In this regard, Applicants have provided an additional reference that further depicts the synthesis of substituted quinolone compounds, particularly directed to substitution at R_{10} through R_{24} with substituents other than hydrogen, and R_2-R_4 with halogen substituents. Specifically, the Examiner's attention is directed to Radl *et al.* "Recent Advances in the Synthesis of Antibacterial Quinolones," Heterocycles, 34:11, (1992) 2143. Radl shows the synthesis of numerous quinolone compounds, including the ***dihalogen substituted compound*** XXI, on page 2149 (*i.e.*, R_2 and R_3 positions are F and Cl respectively),



Radl et al. (XXI)

and the ***trihalogen substituted compound*** LXXXIV on page 2160 (*i.e.*, R_2, R_3, R_4 positions are F),



Radl et al. (LXXXIV)

Applicants agree that a quinolone compound having a heptyl further substituted with multiple substituents is indeed unobvious over the prior art of record. The Applicants, however, ***disagree*** with the assertion that with the teachings of the present invention, corresponding starting materials and the process of making are not readily apparent to one of ordinary skill in the art. One of ordinary skill in the art would have, for example, the references of record available for use in the preparation of the compounds of the invention (including compounds with substituents on the alkylene chain and the ring) eliminating the need for Applicants to specifically disclose within the specification, the preparation of all of the possible compounds within the claimed genus. Therefore, Applicants assert that based on the disclosure of the instant application and art available at the time of filing, the ability to make compounds of the invention ***has*** been enabled. As such, a specific recitation of each compound within the claimed genus is not necessary in the present application.

However, ***at a minimum***, and in accord with the admission of the Examiner on page 11, claim 19, which recites that the compound of claim 1 is 2-heptyl-3-hydroxy-4-quinolone (*i.e.*, the compound that the Examiner admits is enabled), is certainly enabled. Therefore, Applicants respectfully request withdrawal of this rejection.

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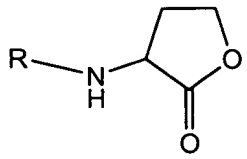
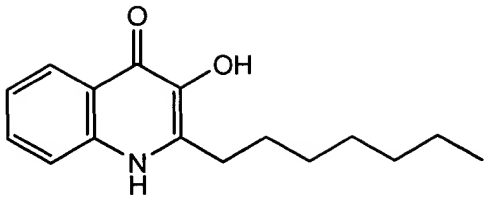
The Office Action further argues that "the high degree of unpredictability is well recognized in the pharmaceutical art, including the autoinducer art." Applicants submit that this statement is clearly not relevant *per se*, to the compound claims that are independent of autoinducer or pharmaceutical activity. As such, the predictability of the pharmaceutical or autoinducer art has no basis with respect to claims 1, 3-13, and 15-19.

In accordance with the invention, these compounds *may* be autoinducers, inhibitors or modulators as those terms are described in the instant application. The application also describes how to characterize the claimed compounds in accordance with these terms.

The Office Action also cites Bycroft's homoserine lactone compounds to illustrate the general unpredictability in the autoinducer art. For the Examiner's convenience, the general structure of Bycroft's homoserine lactone autoinducers is shown below in comparison to the quinolone compounds of the invention.



Bycroft *et al.*



Quinolone Compounds of Invention

However, the Office Action suggests, by the use of Bycroft as the standard of predictability, that the homoserine lactone autoinducers are representative of ***all*** autoinducers, including the quinolone compounds of the invention. Applicants respectfully disagree with this analysis. As is evident by the structural differences of the above-listed structures, homoserine lactones are ***structurally distinct*** from the quinolone compounds of the instant invention.

Additionally, Applicants respectfully submit that the "autoinducer art" in general is overly broad for comparison to the instant application, especially in light of the admission set forth in the Office Action of April 4, 2003, on page 4, indicating that the use of quinolone compounds *as autoinducers* is "***at an infancy stage***." Furthermore, § 2163.03 of the M.P.E.P. states that "[t]he predictability or lack thereof in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention." As such, it is improper to hold Applicants to a standard of an unrelated homoserine lactone art, from which the claimed invention clearly could not be extrapolated from. In fact, ***Bycroft makes absolutely no reference to quinolone compounds or quinolone compounds as autoinducers***. Therefore, assuming, *arguendo*, that the Bycroft reference demonstrates the unpredictability of homoserine lactone compounds, the structural changes and their influence on the activities of the compounds disclosed in Bycroft, is not relevant to the predictability/unpredictability of the activity of the compounds of the instant invention.

Moreover, assuming *arguendo* that the Office Action is correct where it states on page 3 that "[i]t is well known that a small change in the structure of the compound would drastically change its biological activity." By the same reasoning, it would then seem improper that Bycroft's homoserine lactone autoinducers could be used as a "predictive" model for the unpredictability of the Applicants' quinolone autoinducers. More specifically, if small structural changes have large biological effects on homoserine lactones as autoinducers, there should no

basis for comparison between the structural activity of the structures shown above, which have no structural similarity whatsoever.

Additionally, the statement that "the high degree of unpredictability is well recognized in the ***pharmaceutical*** art . . . (Emphasis Added)" on page 3 of the Office Action is even further removed from the realm of the quinolone autoinducer art, which Applicants assert should be the proper art against which comparison should be made. In fact, this comparison seems to stretch the concept of § 2163.03 of the M.P.E.P. to such an extreme that it would not be possible for any pharmaceutical composition to be enabled. Certainly, this interpretation extends beyond the intended scope.

In addition, ***no quinolone art has been cited to support the assertion that the art of quinolone autoinducers is highly unpredictable.*** Without more, Applicants are entitled to a presumption of correctness and operativeness. *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1967); see also, *In re Bowen*, 492 F.2d 859, 181 U.S.P.Q. 48 (C.C.P.A. 1974). The Office Action provides no evidence or relevant art that controverts the assertions made in the instant application

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The Office Action also reiterates that two compounds (described in the instant application on page 24), ***not within the scope of the claims***, further support the presumption of a high degree of unpredictability in that these two compounds did not show autoinducer activity similar to that of 2-heptyl-3-hydroxy-4-quinolone. Applicants respectfully remind the Examiner that claims 1, 3-13, and 15-19 of the instant application are directed to ***compounds per se***, which in turn may have a range of activities, *e.g.*, modulating (both enhancement and inhibition) of the activity of LasR and/or RhlR proteins and quinolone autoinducer compounds (*e.g.*, 2-heptyl-3-hydroxy-4-quinolone), as well as, though ***not necessarily***, autoinducer activity. Thus, at a minimum, this argument is not relevant for the compounds of claims 1, 3-13, and 15-19.

Moreover, the fact that these two compounds did not demonstrate autoinducer activity does not mean that the compounds are not active as modulators (*e.g.*, inhibitors of the autoinducer activity of 2-heptyl-3-hydroxy-4-quinolone). In fact, at page 25, lines 1-2 of the application, Applicants indicate that "these two analogs were not tested in a competitive assay to determine that the analogs did not bind to the PQS". Applicants clearly ***did not exclude the***

possibility that these two compounds could be used as modulators. Therefore, these two compounds do not demonstrate the general unpredictability in the art that the Office Action asserts, and do not make up for the deficiency of Bycroft in providing support for the statement that there is a high degree of unpredictability in the ***quinolone autoinducer*** art.

Furthermore, the Examiner's attention is respectfully drawn to the comments of page 5 of the instant Office Action, which states that "[d]epending on the experimental conditions... the same compound may exhibit weak or undetectable activity." Thus, ***using the Examiner's own reasoning***, the fact that two structurally similar analogs, which are not encompassed by the claims of the instant invention, do not exhibit activity ***in one assay*** does not mean that there is a general unpredictability in the art.

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The Office Action states on page 4 that "[i]n the absence of any specific teachings in the specification on which inventive compound enhances and which inhibits, or both, undue experimentation is required." Applicants again respectfully remind the Examiner that claims 1, 3-13, and 15-19 of the instant application are directed to ***compounds per se***. Therefore, this argument is clearly inapplicable to claims 1, 3-13, and 15-19, as well as claims 20 -28, and 35-48, which do not specify that the compounds are modulators.

Applicants also respectfully submit that specific teachings ***are present*** in the specification with respect to the determination of which compounds of the instant application enhance, and which inhibit. Applicants reiterate that the PQS bioassay has been described on pages 19-23 and in Example 1 on page 28, and using this method and other known methods (*see, e.g.*, U.S. Patent Nos. 5,591,872 and 6,057,288, and in published PCT international patent application Nos. WO 98/57618, WO 98/58075, WO 99/65889, and WO 00/06177), ***one of ordinary skill in the art could, without undue experimentation, determine the type of activity that a compound of the invention possesses***. If the result of the assay shows enhancement, then the compound enhances; and if the result of the assay shows inhibition, then the compound inhibits. Moreover, these are interpretations that are well within the bounds of permissible experimentation.

In particular, the skilled artisan would readily appreciate that modulators of the autoinducer activity of 2-heptyl-3-hydroxy-4-quinolone could be determined without undue experimentation by adding the putative modulator (a compound within the scope of claim 1) to

the bioassay for the PQS as described on page 28 (Example 1), and determining the result of such addition on the autoinducer activity of 2-heptyly-3-hydroxy-4-quinolone by measuring changes in the β-gal readout. ***The skilled artisan would also know that the PQS bioassay would indicate either enhancement or inhibition (or lack of modulation where neither enhancement nor inhibition is indicated by the assay), depending on the results shown in the β-gal readout.*** Additionally, the skilled artisan would understand how to interpret the results of the PQS bioassay, and make a determination as to whether or not the compound is an enhancer or an inhibitor without undue experimentation.

In addition, the Office Action states on page 4 that

> An example for a compound that 'modulates' the activity of PQS, either enhances or inhibits the autoinducer activity of PQS, 'modulates' or antagonize the activity of Las R and/or the Rhl R proteins as recited in the instant claims 29-34 has not been described in the specification. Since the only compound shown is 2-heptyl-3-hydroxy-4-quinolinone[sic] (PQS), and no specific compounds that inhibit or enhance PQS are described, undue experimentation would be required for one of ordinary skill in the art to use the compounds as claimed..

Applicants respectfully disagree. Applicants have already addressed the issue of unpredictability. Moreover, the specification describes a PQS bioassay that was used to examine at least two other compounds (*i.e.*, a demonstration of the utility of this assay). ***The type of activity that a compound of the invention possesses can be easily determined by one of ordinary skill in the art, without undue experimentation, using known methods*** (*see, e.g.*, U.S. Patent Nos. 5,591,872 and 6,057,288, and in published PCT international patent application Nos. WO 98/57618, WO 98/58075, WO 99/65889, and WO 00/06177) and those described in the instant specification (*e.g.*, the PQS assay described on pages 19-23 and in Example 1 on page 28).

In particular, the skilled artisan would readily appreciate that modulators of the autoinducer activity of 2-heptyl-3-hydroxy-4-quinolone could be determined without undue experimentation by adding an alleged modulator (a compound within the scope of claim 1) to the bioassay for the PQS as described on page 28 (Example 1), and determining the result of such addition on the autoinducer activity of 2-heptyly-3-hydroxy-4-quinolone by measuring changes in the β-gal readout.

In regard to claims 32-34, the LasR and RhlR proteins are the well-reputed autoinducer transcriptional regulator proteins as described in the Background section of the specification on page 2 lines 33-34. Therefore, it would be clear to one of ordinary skill in the art that modulators of the LasR and/or RhlR proteins could be determined by measuring the affect of the addition of quorum signaling molecules associated with the activity of these proteins; *i.e.*, modulators of LasR would affect the response to exogenously added N-(3-oxododecanoyl) homoserine lactone, while the modulators of RhlR would affect the response to exogenously added N-butyryl homoserine lactone. Support for this assertion is set forth in the application on page 2, lines 33-39 and pages 19-21, in the section of the specification entitled "Discovery of a Novel Cell-to-Cell Signal".

It appears that the Office Action insists, and in fact relies, upon the notion that there is a greater burden for disclosure in this case, based on the presumption of a "high degree of unpredictability in the autoinducer art." However, as discussed above, the Examiner has failed to prove that, in fact, there ***is*** a high degree of unpredictability in the ***quinolone autoinducer art***, which Applicants contend is the appropriate art for comparison with respect to predictability.

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Finally, it is the Applicants' understanding that in establishing enablement, the *Wands* fators must be evaluated for each claim in question. In particular, the M.P.E.P. states in § 2164.01(a), that

> [i]t is ***improper*** to conclude that a disclosure is not enabling ***based on an analysis of only one of the above factors while ignoring one or more of the others***. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407. (Emphasis Added)

The Office Action has generally identified the set of claims to which this rejection applies as "all pending claims," and has generally applied certain elements of certain of the *Wands* factors. Moreover, Applicants have shown that any analysis of certain *Wands* factors discussed in the Office Action is, at the very minimum, inapplicable to certain claims. In this regard, Applicants respectfully request further clarification.

In view of the foregoing, Applicants submit that the claims 1-42 and 46-48 are fully enabled by the specification, and respectfully request reconsideration and withdrawal of the rejection of these claims under §112, first paragraph.

Claim Rejections - 35 U.S.C. §102

Rejection of Claims 1, 4, 10-14, 19-28, 32-42, 46-48 under 35 U.S.C. §102(b)

The rejection of claims 1, 4, 10-14, 19-28, 32-42 and 46-48 under 35 U.S.C. §102(b) as anticipated by Takeda (Hakko Kogaku Zasshi, 1959, 37, 59-63) was maintained for reasons of record. Moreover, the Examiner states that "the prior art compound ... is identical to the instant compound." Applicants respectfully disagree.

In support of this argument, the Applicants invite the Examiner's attention to the last sentence of the cited abstract, which states, "[t]he substance B-A was ***suggested*** to be 2-heptyl-3-hydroxy-quinolone." (emphasis added) By this statement, Takeda *et al.* merely speculates as to the actual structure of substance B-A. In addition, the Examiner's attention is directed to Takeda's "substance B-A," which has a melting point range of ***182-185 °C***. ***In contrast, the instant specification at page 30, line 11, discloses that the melting point range of 2-heptyl-3-hyroxy-4-quinolone (identified by NMR, HPLC, and low and high resolution mass spectrometry) is 196-198 °C***. Applicants assert that if the Takeda compound, which is merely ***suggested*** to be 2-heptyl-3-hyroxy-4-quinolone, is in fact identical to that of the instant invention, then it would have a melting point range at least similar, if not identical to that of the 2-heptyl-3-hyroxy-4-quinolone compound of the instant invention. Moreover, the mean melting point temperatures differ by 13.5 °C. Accordingly, substance B-A clearly cannot be 2-heptyl-3-hyroxy-4-quinolone.

The Office Action further states that depending on the experimental conditions and the purity of the compound, the same compound may exhibit weak or undetectable activity. Yet, the Examiner provides no reference which supports this argument. Moreover, without such support, this argument is nothing more than speculation by the Examiner, which is improper.

However, assuming arguendo that such speculation is allowable, Applicants assert that the determination of purity from melting point, *i.e.*, that a small melting point range indicates a pure compound, is known by the ordinarily skilled artisan. Applicants also submit that the 2-

heptyl-3-hyroxy-4-quinolone isolated in Example 3 of the present invention, or alternatively synthesized in Example 5 of the present invention, is pure based on the corresponding NMR data/spectrum depicted on page 23 of the instant specification. Furthermore, Applicants note that the melting point range for the pure 2-heptyl-3-hyroxy-4-quinolone was 2°C. The similarly narrow melting point range of Takeda's substance B-A, 3°C, would seemingly also be indicative of a nearly pure compound. Accordingly, the purity of the sample should ***not*** be considered as a factor that would introduce weak anti-*Staphylococcus aureus* activity. In this regard, Applicants reiterate that Takeda's substance B-A exhibited anti-*Staphylococcus aureus* activity, whereas 2-heptyl-3-hyroxy-4-quinolone did not, as noted on page 27, lines 3-5 of the instant specification. As such, it cannot be assumed that the two are identical compounds.

Applicants also note that Takeda states that substances B-B, which was separated into **eight (8)** compounds, and substance C, were also isolated from the culture using similar procedures. This provides clear evidence that there are a number of compounds that could be isolated from extract of *Pseudomonas aeruginosa*; and thus, to assume that substance B-A and 2-heptyl-3-hyroxy-4-quinolone are identical compounds merely because they were both isolated from *Pseudomonas aeruginosa* would be inappropriate.

The Office Action states that

> [o]nce... a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). See also MPEP §716.07.

In light of the foregoing argument, ***Applicants submit that a clear showing that Takeda's substance B-A is not 2-heptyl-3-hyroxy-4-quinolone has been made, which rebuts the presumption of operability***. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 USC § 102(b) of claims 1, 4, 10-14, 19-28, 32-42 and 46-48. In addition, Applicants respectfully point out that claim 14 has been deleted, and therefore suggest that the rejection of claim 14 under 35 U.S.C. §102(b) is moot.

Specification/Drawings

The specification has been objected to because the figures in the specification do not come within the purview of 37 CFR 1.58(a). The Office Action further states that formal drawings are required as well as a brief description of drawings. Applicants reiterate that this issue will be addressed by Applicants upon allowance of claims

Claim Rejections - 35 U.S.C. §112

Rejection of Claims 14-16 under 35 U.S.C. §112, Second Paragraph

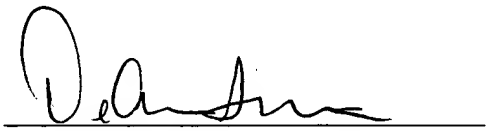
Claims 14-16 have been rejected under 35 U.S.C. §112, first paragraph, as being indefinite for failing to particularly point our and distinctly claim the subject matter which Applicants regard as the invention. Applicants have cancelled claim 14 and have amended claims 15 and 16 to adjust the dependency from cancelled claim 14 to a dependency from claim 1. Accordingly, Applicants respectfully request that this rejection be withdrawn.

SUMMARY

In view of the foregoing, entry of the amendments and remarks presented herein, reconsideration and withdrawal of all the objections and rejections, and allowance of the application with all pending claims are respectfully requested. If a telephone conversation with Applicant's attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP



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